REVIEW ARTICLE

Lipid Management in Patients with Type 2 Diabetes

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Background: Diabetes is correlated with a high risk for cardiovascular disease (CVD). The management of diabetic dyslipidemia, a well-recognized and modifiable risk factor, is a key element in the multifactorial approach to preventing CVD in patients with type 2 diabetes. Diabetic dyslipidemia is characterized by elevated triglyceride levels, decreased high-density lipoprotein cholesterol levels, and elevated low-density lipoprotein cholesterol (LDL-C) levels.

Objectives: To describe the effective approach to the management of dyslipidemia in patients with diabetes to allow providers and payers to become familiar with the treatment goals for all the components of lipoproteins, to correctly initiate appropriate lipid-lowering medications based on treatment goals and lipid-lowering capability, and to apply the data presented in lipid clinical trials to the treatment of patients with diabetes.

Summary: Diabetes is associated with a 2- to 4-fold increase in risk for CVD. The risk factors for coronary artery disease (CAD) include hypertension, dyslipidemia, obesity, and smoking. Therefore, prioritizing and managing diabetic patients with CVD risk factors is vital.

Conclusion: LDL-C appears to have the greatest role in premature and early atherosclerosis and the development of CAD and must be treated as aggressively as hyperglycemia to reduce CAD risk. Becoming familiar with lipid treatment goals and the many therapies available today can help providers and payers implement the appropriate approach to managing diabetic dyslipidemia risk factors and reduce the burden of this disease.

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The prevalence of diabetes has increased dramatically in recent decades. This trend highlights the importance of prevention and appropriate therapy to reduce cardiovascular events in patients with diabetes. Reaching adequate blood glucose control is important in decreasing microvascular complications associated with diabetes; however, good lipid management is vital for reducing the incidence of cardiovascular events in patients with diabetes.[1-4]

Cardiovascular disease (CVD) has been recognized as the most frequent cause of morbidity and mortality among those with diabetes. Diabetes is associated with a 2- to 4-fold increased risk for CVD and is identified as a coronary artery disease (CAD) risk equivalent.[1-4]

The risk factors for CAD include hypertension, dyslipidemia, obesity, and smoking.[1-3] Therefore, prioritizing and managing diabetic patients with CVD risk factors is extremely important. In dyslipidemia, serum low-density lipoprotein cholesterol (LDL-C) appears to have the greatest role in premature and early atherosclerosis and CAD development and must therefore be treated as aggressively as hyperglycemia to reduce CAD risk. In fact, improved control of LDL-C can reduce cardiovascular complications by 20% to 50%.[5]

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Diabetic Dyslipidemia

Diabetic dyslipidemia is characterized by elevated triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), and elevated LDL-C in comparison with patients without diabetes. HDL-C is responsible for removing excess cholesterol from the peripheral tissues.[1-4] Therefore, when HDL-C is decreased, triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and LDL-C levels will all be elevated.[1-4]

The particle size of LDL-C contributes to these elevations. In patients with diabetes, the particle size of LDL-C is much smaller and denser because of elevated triglyceride levels, which in turn contributes to a 3-fold increase in the risk for developing CAD. The mechanism responsible for this process is triggered by the particles' ability to enter the blood vessels much more quickly than do normal, large, and less-dense LDL-C particles, thereby increasing the risk for thrombosis.[1]

Elevated triglyceride levels can arise from 2 abnormalities—overproduction of VLDL-C and impaired

lipolysis of triglycerides. Patients with type 2 diabetes have an overproduction of triglyceride-rich VLDL-C level, which is a result of high free fatty acid levels, hyperglycemia, obesity, and insulin resistance. In fact, approximately 30% to 40% of patients with diabetes have triglyceride levels >200 mg/dL, and 10% of patients have triglyceride levels >400 mg/dL.[1-4]

LDL-C Treatment Goals

Lowering LDL-C is the main goal of treatment. The specific LDL-C treatment goals are outlined in **Table 1**. Once the LDL-C goal is attained, other lipid and non-lipid risk factors can be addressed. Therapeutic lifestyle changes are considered first-line therapy and should be continued for at least 3 months before initiating pharmacotherapy.[6] Drug therapy should be reserved for patients who are at increased risk for CAD or for those in whom lifestyle changes alone are ineffective. The Framingham risk scoring system should be used for individuals with no evidence of CAD but with 2 or more major risk factors for CAD other than LDL-C.[6,7]

In high-risk individuals, the initiation of drug therapy

KEY POINTS

- Diabetes is correlated with a high risk for cardiovascular disease (CVD).
- Managing diabetic dyslipidemia—characterized by elevated triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), and elevated low-density lipoprotein cholesterol (LDL-C) levels—is a crucial aspect of the multifactorial approach to preventing CVD in patients with type 2 diabetes.
- LDL-C has the greatest role in early atherosclerosis and must be treated as aggressively as hyperglycemia to reduce coronary artery disease risk.
- Providers and payers must become familiar with current treatment lipid goals, including the management of elevated LDL-C levels, reduced HDL-C levels, and elevated triglyceride levels.
- Therapeutic lifestyle changes should be attempted before instituting pharmacotherapy. The appropriate use of the many medications available for diabetic dyslipidemia can help reduce the burden of this disease and the risk for CVD.

Table 1 Current LDL-C Treatment Goals

Risk category	LDL-C goal	LDL-C threshold for initiating TLCs	LDL-C threshold for drug therapy
CHD risk equivalents, 10-yr risk >20%: • Age >45 yrs in men, >55 yrs in women • Smoking • HTN or taking antihypertensives • HDL-C <35 mg/dL • Diabetes • Family history of CHD	<100 mg/dL Optional, <70 mg/dL	≥100 mg/dL	≥100 mg/dL For <100 mg/dL, consider initiating or intensifying LDL-C–lowering therapy Treat other risk factors or use other lipid-modifying drugs if high TG or low HDL-C
2+ risk factors (10-yr risk, 10%-20%)	<130 mg/dL Optional, <100 mg/dL	≥130 mg/dL	≥130 mg/dL For 100-129 mg/dL, consider LDL-C– lowering therapy
2+ risk factors (10-yr risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
0-1 risk factor (10-yr risk not needed)	<160 mg/dL	≥160 mg/dL	≥190 mg/dL For 160-189 mg/dL, drug therapy is optional Consider therapy if single severe risk factor, multiple life habits and/or emerging risk factors, or 10-yr risk is nearly 10%

NOTE: Use the Framingham scoring system to identify those with a 10-year risk.
CHD indicates chronic heart disease; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TLCs, therapeutic lifestyle changes.
Source: Reference 6.

Table 2 LDL-C versus Non–HDL-C Treatment Goals

Risk category	LDL-C goal	Non–HDL-C[a] goal
CHD and CHD risk equivalents (10-yr risk >20%)	<100 mg/dL	<130 mg/dL
2+ risk factors (10-yr risk ≤20%)	<130 mg/dL	<160 mg/dL
0-1 risk factor	<160 mg/dL	<190 mg/dL

[a]Total cholesterol minus HDL-C.
CHD indicates chronic heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Source: Reference 6.

Table 3 Management of High Triglycerides

Classification	TG level	On top of achieving target LDL-C goal
Normal	<150 mg/dL	
Borderline high	150-199 mg/dL	Reduce weight, increase physical activity
High	200-499 mg/dL	Intensify LDL-C–lowering therapy or initiate nicotinic acid or a fibrate
Very high	≥500 mg/dL	Goal is to prevent acute pancreatitis through TG-lowering by using very-low-fat diets, weight reduction, increased physical activity, and a TG-lowering agent When TG level is ≤500 mg/dL, focus on lowering LDL-C

LDL-C indicates low-density lipoprotein cholesterol; TG, triglyceride.
Source: Reference 6.

should be considered to achieve the non–HDL-C goal (**Table 2**).[6] This can be accomplished by intensifying therapy with an LDL-C–lowering drug or by adding nicotinic acid or a fibrate.

Elevated triglyceride levels is an independent risk factor for CAD. For all patients with high triglyceride levels, the primary goal of therapy is to achieve the target goal for LDL-C (**Table 3**).[6]

Management of Low HDL-C

Low HDL-C (<40 mg/dL) is a strong predictor of CAD.[6] However, there is no specific goal for increasing HDL-C. After the LDL-C goal is achieved, weight loss and increased physical activity should be emphasized, and non–HDL-C levels should be evaluated if the triglyceride level is high. If the triglyceride level is at goal, medications for raising HDL-C, such as fibrates or nicotinic acid, should be considered.

Pharmacologic Treatment

HMG-CoA Reductase Inhibitors (Statins)

The 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, or statins, are the most extensively used lipid-lowering medications and are often the first choice for the treatment of diabetic dyslipidemia (**Table 4**).[1] Statins primarily lower LDL-C levels, but they also have the secondary effects of lowering triglyceride and increasing HDL-C levels. Furthermore, statins may increase the particle size of LDL-C to allow less circulation of smaller, dense LDL-C.[1]

Mechanism of action. Statins competitively inhibit HMG-CoA reductase, converting HMG-CoA to mevalonate in the hepatic synthesis of cholesterol; the overall result is decreased levels of endogenous cholesterol. Because of the decreased endogenous cholesterol levels, LDL-C receptor synthesis is activated, resulting in enhanced clearance of circulating LDL-C.[1]

Dosing and administration. Statins are generally administered in the evening (with or without food) or at bedtime to coincide with the time of day when cholesterol synthesis generally occurs. Initial therapy starts with a lower dose and is generally titrated every 4 to 6 weeks as warranted to achieve the necessary maximum dosage and to decrease the risk for adverse effects.[1]

Precautions, contraindications. Statins are contraindicated in pregnant and breastfeeding women and should be used with caution in patients with impaired renal/hepatic function.[1]

Adverse effects. Overall, statins are well tolerated and have negligible adverse effects. The more common adverse effects are headache, nonspecific muscle and joint pain, nausea, diarrhea, constipation, flatulence, and abdominal pain. Significant elevation of liver enzymes can occur, and the discontinuation of treatment is recommended when liver enzymes reach ≥3 times the upper limit of normal.[1]

Myopathy, a disease of muscle, and rhabdomyolysis, the breakdown of striated muscle, have been reported in 1% to 5% of patients taking statins.[1] Patients are encouraged to immediately report any unexplained muscle weakness, tenderness, pain, or fever. An elevated serum creatinine kinase—between 450 IU/L and >1000 IU/L, which is 3 to 10 times the upper limits of normal—can be observed in myopathy or myositis, respectively.[1]

Rhabdomyolysis, a more severe adverse effect, typi-

Table 4 Comparing Lipid-Lowering Effects of Statins and Daily Cost of Therapy

Drug (brand)	Daily dose, cost[a]	Total cholesterol change from baseline, %	LDL-C change from baseline, %	TG change from baseline, %	HDL-C change from baseline, %
Atorvastatin (Lipitor)					
	10 mg, $3.66	–29	–39	–19	6
	20 mg, $4.99	–33	–43	–26	9
	40 mg, $4.99	–37	–50	–29	6
	80 mg, $4.99	–45	–60	–37	5
Fluvastatin (Lescol)					
	20 mg, $3.91	–17	–22	–12	3
	40 mg, $3.63	–19	–25	–14	4
	40 mg bid, $7.26	–27	–36	–18	6
	XL, 80 mg, $4.82	–25	–35	–19	7
Lovastatin (Mevacor)					
	10 mg, $1.06	–16	–21	–10	5
	20 mg, $0.76	–17	–24	–10	6
	40 mg, $1.19	–22	–30	–14	7
	40 mg bid, $2.38	–29	–40	–19	9
Pravastatin (Pravachol)					
	10 mg, $0.63	–16	–22	–11	7
	20 mg, $0.93	–24	–32	–15	12
	40 mg, $0.86	–25	–34	–20	15
	80 mg, $3.99	–27	–37	–19	3
Rosuvastatin (Crestor)					
	5 mg, $5.16	–33	–45	–35	13
	10 mg, $5.16	–36	–52	–10	14
	20 mg, $5.19	–40	–55	–28	8
	40 mg, $5.23	–46	–63	–2	10
Simvastatin (Zocor)					
	5 mg, $0.59	–19	–26	–12	10
	10 mg, $0.66	–23	–30	–15	12
	20 mg, $0.93	–28	–38	–19	8
	40 mg, $0.93	–31	–41	–18	9
	80 mg, $1.19	–36	–47	–24	8
Pitavastatin (Livalo)					
	1 mg, $3.65	–23	–32	–15	8
	2 mg, $3.65	–26	–36	–19	7
	4 mg, $3.65	–31	–43	–18	5

[a]Cost as reported by drugstore.com.

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Adapted with permission from Cornell S, Vito CJ. Pharmacologic therapies: dyslipidemia and hypertension in persons with diabetes. In: Mensing C, ed. *The Art and Science of Diabetes Self-Management Education: A Desk Reference for Healthcare Professionals*. Chicago, IL: American Association of Diabetes Educators; 2006:399-412.

Table 5 Lipid-Lowering Effects of Bile Acid Sequestrants

Drug (brand)	Daily dose, cost	Total cholesterol, change from baseline, %	LDL-C, change from baseline, %	TG, change from baseline, %	HDL-C, change from baseline, %
Cholestyramine (Questran)					
	4-8 g bid, $4.08	N/A	–15 to –30	5-10	3-5
Colestipol (Colestid)					
	30 g (powder), $2.86	N/A	–15 to –30	5-10	3-5
	16 g (tablets), $0.88	N/A	–15 to –30	5-10	3-5
Colesevelam (Welchol)					
	3.8 g (powder), $8.10	–7	–15	10	3
	1875 mg bid, $0.75	–7	–15	10	3

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not available; TG, triglyceride.
Sources: Reference 1; www.drugstore.com.

cally presents with additional symptoms, including weight gain from fluid retention, fever, nausea, tachycardia, and dark-colored urine.[1]

Drug interactions. Most statins are metabolized via the cytochrome (CY) P450 3A4 pathway in the liver. Medications and foods, such as grapefruit juice (>8 oz daily), that are also metabolized through the CYP450 3A4 system should be monitored for increased levels and risks for adverse reactions.[1]

Monitoring. A baseline lipid profile, serum creatinine kinase, liver function tests, and serum creatinine should be obtained before initiating statin therapy. Monitoring lipid profiles and liver function tests should be conducted every 3 months in the first 6 months of treatment and periodically thereafter. Serum creatinine kinase levels should be checked if a patient reports any muscle pain or discomfort.[1]

New safety precautions for simvastatin. On June 8, 2011, the US Food and Drug Administration (FDA) recommended new limits for the use of simvastatin 80 mg, because of increased risk of muscle damage.[8] Therefore, simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of myopathy. Simvastatin 80 mg should not be started in new patients, including those already taking lower doses of the drug.[8]

In addition to these new limitations, the FDA also required the simvastatin label to include new contraindications and dose limitations for using simvastatin with certain medicines.[8] Furthermore, as of that time, simvastatin is contraindicated with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol.[8]

Also, simvastatin daily doses should not exceed 10 mg when coadministered with amiodarone, verapamil, or diltiazem. (These drugs are contraindicated with niacin/simvastatin, because that combination is only available with simvastatin 20 or 40 mg.) A simvastatin daily dose of 20 mg should not be exceeded when used concurrently with amlodipine or with ranolazine.[8]

Bile Acid Sequestrants

LDL-C is the primary lipoprotein affected by bile acid sequestrants (**Table 5**), which also produce a secondary effect of a small increase in HDL-C. Bile acid sequestrants often increase triglycerides, which are already elevated in many patients with diabetes. Therefore, bile acid sequestrants should be avoided as monotherapy in patients with high triglycerides (>250 mg/dL).[1]

Mechanism of action. Bile acid sequestrants bind to bile acids in the intestinal lumen, thereby decreasing the production of cholesterol. They also inhibit enterohepatic circulation of bile acids and increase the elimination of fecal acid steroids, resulting in a decrease in LDL-C.[1]

Dosing and administration. Bile acid sequestrants can be dosed once or twice daily. Lower doses are initiated and can be titrated up every 1 to 2 months, as warranted, to achieve the optimal or maximum dose. Tablets should be swallowed whole and taken with plenty of fluid.[1]

Precautions and contraindications. Colesevelam is listed as pregnancy category B, which indicates that there is no evidence of risk to humans. Cholestyramine and colestipol are listed as pregnancy category C, indi-

Table 6 Lipid-Lowering Effect of Cholesterol Absorption Inhibitor

Drug (brand)	Daily dose, cost	Total cholesterol change from baseline, %	LDL-C change from baseline, %	TG change from baseline, %	HDL-C change from baseline, %
Ezetimibe (Zetia)	10 mg, $4.50	–13	–18	–8	1

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
Sources: Reference 1; www.drugstore.com.

cating that risk cannot be ruled out. Bile acid sequestrants are contraindicated when the triglyceride level is >400 mg/dL with primary biliary cirrhosis and bowel and biliary obstructions. Caution should be used in patients with renal insufficiency, volume depletion, and chronic constipation.[1]

Adverse effects. Most adverse effects are gastrointestinal (GI), because of a lack of systemic absorption. The most common adverse effects are headache, unpalatable taste, nausea, bloating, flatulence, and constipation.[1]

Drug interactions. Bile acid sequestrants can bind to other medications, resulting in decreased absorption of the other medications and in clinically significant drug interactions. Therefore, it is advised to separate bile acid sequestrants from other medications by administering them 1 hour before or 4 hours after the bile acid sequestrants. Prolonged use of bile acid sequestrants may result in a decrease in absorption of fat-soluble vitamins and folic acid.[1]

Monitoring. A baseline lipid profile, with a follow-up at 4 to 6 weeks for efficacy, is advised. Electrolytes should be routinely checked, because imbalances have been reported. Prolonged use of bile acid sequestrants may produce hyperchloremic acidosis. Because of the GI adverse effects reported with bile acid sequestrants, patient compliance should be assessed at every visit.[1]

Cholesterol Absorption Inhibitors

The primary effect of cholesterol absorption inhibitors is evaluated in the decrease of LDL-C; however, small decreases in triglyceride levels and increases in HDL-C may be noticed. Cholesterol absorption inhibitors are often prescribed in combination with statins to enhance the lowering of LDL-C (**Table 6**).[1]

Mechanism of action. Cholesterol absorption inhibitors selectively inhibit the absorption of cholesterol from the small intestine, resulting in a reduced delivery of cholesterol to the liver and decreased hepatic cholesterol stores, thereby lowering cholesterol levels, primarily LDL-C.[1]

Dosing and administration. The initial and maintenance dose is 10 mg daily, in conjunction with a statin or bile acid sequestrants. Tablets can be taken with or without food.[1]

Precautions and contraindications. Ezetimibe is listed as pregnancy category C and should be avoided to reduce risks. Caution should be used in patients with hepatic dysfunction.[1]

Adverse effects. Ezetimibe is generally well tolerated and has very few adverse effects. The most common complaints include GI disorders, such as diarrhea and abdominal pain, as well as back pain, arthralgia, and sinusitis.[1]

Drug interactions. Bile acid sequestrants may hinder absorption of ezetimibe. Therefore, ezetimibe should be administered 1 hour before or 4 hours after the bile acid sequestrant, if it is used concomitantly. Fibrates can increase cholesterol excretion into the bile; therefore, concurrent use is not advised.[1]

Monitoring. A baseline lipid profile and liver function tests should be performed before initiating therapy. When ezetimibe is used in combination with a statin, liver enzymes should be monitored before initiating statin therapy, every 3 months in the first 6 months of treatment and periodically thereafter. An international normalized ratio (INR) should also be monitored in patients taking warfarin.[1]

Fibrates

The primary lipid-lowering effect of fibrates is on triglyceride levels. Fibrates also have an additional effect of increasing HDL-C level (**Table 7**).[1]

Mechanism of action. The manner in which fibrates exert their lipid-lowering effect is unclear. However, these agents can increase lipoprotein lipase, thereby breaking down VLDL. Fibrates also decrease hepatic VLDL synthesis while enhancing the removal of triglyceride-rich lipoproteins.[1]

Dosing and administration. Fibrates are generally dosed once to twice daily, often 30 minutes before a meal or with a meal. Lower doses are initiated and can be titrated up every 1 to 2 months, as warranted, to achieve the optimal or maximum dose.[1]

Precautions and contraindications. Fibrates are listed as pregnancy category C and should be avoided to

reduce risks. Caution and lower doses should be used in the elderly and patients with renal dysfunction.[1]

Preexisting gallbladder disease, hepatic dysfunction, and severe renal dysfunction are contraindications for fibrate use.[1]

Adverse effects. Fibrates are generally well tolerated and have very few adverse effects. The most common complaints are GI, including indigestion, nausea, diarrhea, flatulence, and abdominal pain. Rare adverse effects include rash, fever, weight gain, muscle weakness, drowsiness, decreased potassium levels, anemia, and low white blood cell count.[1]

Drug interactions. Fibrates are highly protein bound and can increase the adverse effects of medications that are also highly protein bound, such as warfarin, sulfonylureas, and meglitinides.[1]

Monitoring. Triglycerides and cholesterol levels should be measured before initiating fibrate therapy and at 3- to 6-month intervals. Liver function tests and a complete blood cell count should also be evaluated at baseline and 6-month intervals. Fibrate therapy should be discontinued when liver enzymes are >3 times the upper limit of normal.[1]

Hematologic changes, such as decreased hemoglobin and hematocrit, thrombocytopenia, and neutropenia, should be monitored. If fibrates are to be used concurrently with statins, sulfonylureas, warfarin, or bile acid sequestrants, close monitoring is warranted to decrease the risks of hypoglycemia and increased INR.[1]

Niacin

The primary effect of niacin is an increase in HDL-C, with a small decrease in triglyceride levels and LDL-C. Although niacin increases HDL-C levels, it can also increase blood glucose levels, especially in patients with prediabetes and in those with newly diagnosed diabetes (**Table 8**).[1]

Mechanism of action. Niacin reduces the catabolism

Table 7 Lipid-Lowering Comparison of Fibrates

Drug (brand)	Daily dose, cost	Total cholesterol change from baseline, %	LDL-C change from baseline, %	TG change from baseline, %	HDL-C change from baseline, %
Fenofibrate(Tricor)	145 mg, $5.59	–18	–20	–29	11
Gemfibrozil(Lopid)	600 mg bid, $0.38	–10	±10	–20 to –50	10-15

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
Sources: Reference 1; www.drugstore.com.

Table 8 Lipid-Lowering Effects of Niacin

Drug (brand)	Daily dose, cost	Total cholesterol, change from baseline, %	LDL-C, change from baseline, %	TG, change from baseline, %	HDL-C, change from baseline, %
Niacin					
	1000 mg, $0.11	N/A	–6	N/A	N/A
	1500 mg, $0.11	N/A	–12	N/A	N/A
	2000 mg, $0.11	N/A	–16	N/A	N/A
Extended-release niacin (Niaspan)					
	500 mg, $2.93	–2	–3	–5	10
	1000 mg, $4.99	–5	–9	–11	15
	1500 mg, $7.80	–11	–14	–28	22
	2000 mg, $9.99	–12	–17	–35	26

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not available; TG, triglyceride.
Sources: Reference 1; www.drugstore.com.

Table 9 Lipid-Lowering Effect of Omega-3 Fatty Acid

Drug (brand)	Daily dose, cost	Total cholesterol, change from baseline, %	LDL-C change from baseline, %	TG, change from baseline, %	HDL-C, change from baseline, %
Omega-3 fatty acid (Omacor)					
	1 g, $1.57	N/A	10	–3.5	13
	2 g, $1.57	N/A	31	–45	13

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not available; TG, triglyceride.
Sources: Reference 1; www.drugstore.com.

of HDL-C and selectively decreases the excretion of HDL-C. In addition, niacin reduces hepatic VLDL-C production, which results in a decrease of LDL-C and triglyceride levels.[1]

Dosing and administration. Niacin is available in immediate-release, sustained-release, and extended-release formulations and should not be interchanged. Immediate-release niacin is preferred over sustained-release niacin, because of unfavorable adverse effects.[1]

For immediate-release niacin, doses as low as 100 mg 3 times daily can be gradually titrated to 3 g daily in divided doses. For sustained-release niacin, doses as low as 250 mg twice daily can be titrated to 2 g daily in a single or divided dose. Niacin should be taken 30 minutes after an aspirin or with a low-fat snack to minimize flushing effects. Niacin should not be taken with hot beverages or with alcohol.[1]

Precautions and contraindications. Niacin is listed as pregnancy category C and should be avoided during pregnancy. Caution should be used in patients with preexisting gout, a history of heavy alcohol use, or renal dysfunction. Liver dysfunction, active peptic ulcer disease, and arterial bleeding are contraindications.[1]

Adverse effects. The most common complaints are headache, hypotension, and GI discomfort, such as nausea, vomiting, diarrhea, flushing, pruritus, and rash. Flushing usually dissipates with continuous use and can be reduced by taking niacin with meals. Aspirin taken once daily 30 minutes before the niacin dose can also minimize flushing. Patients taking >2 g of niacin daily may be at risk for hepatotoxic effects. Treatment should be discontinued when liver enzymes are >3 times the upper limit of normal.[1]

Drug interactions. Alcohol and hot drinks can increase the flushing and pruritus adverse effects. Rhabdomyolysis may occur when used in combination with statins.[1]

Monitoring. A baseline lipid profile, liver function, uric acid, and blood glucose levels should be performed before initiating niacin therapy and repeated at 6-week intervals while adjusting the dose. Lipid profiles should be reviewed at 3- to 6-month intervals. Blood glucose levels should be monitored regularly, especially in those with newly diagnosed diabetes or with prediabetes. Liver enzymes should also be monitored at 3-month intervals during the first year of treatment.[1]

Omega-3 Fatty Acids

Lowering triglyceride levels is the primary effect of omega-3 fatty acids (**Table 9**). Increased HDL-C level is a secondary benefit, but this occurs only when high doses are used. LDL-C levels tend to increase, which is dose related.[1]

Mechanism of action. Omega-3 fatty acids exert their effect by reducing hepatic VLDL-C production. They also reduce the quantity of free fatty acids available for triglyceride synthesis, thereby lowering VLDL-C synthesis and increasing lipoprotein lipase activity, resulting in triglyceride clearance.[1]

Dosing and administration. The initial dose of omega-3 fatty acids is one to two 1000-mg capsules daily and can be titrated up to a maximum dose of 4 g daily. Omega-3 fatty acid should be taken with food to minimize GI adverse effects.[1]

Precautions and contraindications. There are no adequate studies in pregnant women; therefore, omega-3 fatty acids should be avoided during pregnancy. Caution should be used in patients with renal or hepatic dysfunction, the elderly, and those at high risk for hemorrhage.[1]

Adverse effects. The most common adverse effects are dizziness and GI discomfort, such as dyspepsia, nausea, and abdominal pain. Rare adverse effects include headache, pruritus, and hyperglycemia.[1]

Drug interactions. Omega-3 fatty acids may decrease the production of thromboxane A_2, resulting in an increase in bleeding time. Omega-3 fatty acids taken in combination with warfarin therapy can increase the INR.[1]

Table 10 Clinical Trials Using Statin Therapy

See print issue.

Monitoring. A baseline lipid profile and liver function tests should be performed before initiating omega-3 fatty acid therapy and repeated at regular intervals, while adjusting dosage. Patients taking warfarin should have their INR monitored for increases in bleeding time.[1]

Table 10 (available in the print issue only) displays the results of 7 major clinical trials using statin treatment, which specifies the type and dose of statin used, the baseline LDL-C, the number of patients with diabetes versus the total number of participants, CVD outcome, and relative risk reduction for patients with diabetes versus those without.

Relative risk reduction determines an appropriate treatment plan, by accounting not only for the effectiveness of a proposed treatment but also for the relative likelihood of an incident (positive or negative) occurring in the absence of treatment.

The clinical trials are further divided by primary and secondary prevention. Primary prevention involves preventing risk factors that lead to chronic diseases, infections, and injuries. Secondary prevention is aimed to prevent further exacerbation of a known problem.

Conclusion

Becoming familiar with lipid treatment goals and the many therapies available today can help providers and payers implement the appropriate approach to the management of the risk factors associated with diabetic dyslipidemia and reduce the burden of this disease.

Treatment goals and strategies for diabetic dyslipidemia must be given equal importance and must be as aggressive as those developed for hyperglycemia. The primary lipoprotein target is LDL-C; however, triglycerides, HDL-C, and particle size of LDL-C must be addressed in the treatment plan. The goal of initiating drug therapy is to achieve optimal levels of these lipoproteins. Combinations of lipid-lowering agents are often warranted to achieve this goal. Adding medications to existing regimens requires patients to change their behavior. Therefore, the patient's readiness for change and the level of conviction and confidence must be evaluated.

The use of precombined medications can be beneficial for patients who are not willing to take more medications. Statins are traditionally the first medication of choice in diabetic dyslipidemia. However, the addition of a cholesterol absorption inhibitor (eg, ezetimibe) can enhance lowering of LDL-C, and fibrates can reduce triglyceride levels and raise HDL-C levels. Two or more lipid-lowering medications may be necessary for some patients. Lipid profiles, liver enzymes, and adverse effects, as well as patient adherence must be routinely monitored. Lipid management may be challenging at times in patients with diabetes, but educating patients and getting them involved in the treatment plan may lead to more productive results. ■

Author Disclosure Statement

Dr Daniel reported no conflicts of interest.

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STAKEHOLDER PERSPECTIVE

The Time Is Now to Promote Aggressive Lipid Management to Prevent Macrovascular Complications in Patients with Type 2 Diabetes

MEDICAL DIRECTORS: Type 2 diabetes is a major area of concern for health plans. With the rising tide of obesity in the United States, we are set to experience an unprecedented portion of the population who will develop type 2 diabetes, in particular among the elderly. The cost of caring for the diabetic patient is largely driven by the complications of the disease. In this article by Dr Daniel, we are reminded that control of hemoglobin (Hb) A_{1c} is only part of the diabetic story. Although good control of HbA_{1c} will help prevent microvascular complications of the disease, macrovascular complications are largely unaffected by

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STAKEHOLDER PERSPECTIVE *(Continued)*

such tight control. We are further reminded by Dr Daniel that management of lipid disorders, especially the management of low-density lipoprotein cholesterol (LDL-C) levels, will ultimately produce improvement in or prevent potential macrovascular complications of diabetes, such as myocardial infarction and stroke.

Therefore, the focus of health plans on the management of diabetes and its associated complications must go beyond the reduction of HbA_{1c} levels. At a minimum, diabetic management programs need to include lifestyle modifications, weight management programs, exercise counseling, disease education, and medication adherence programs. Drug therapy to lower LDL-C levels is one of the cornerstone treatments for the management of the diabetic patient. Health plans must promote aggressive lipid management in a cost-effective manner to help patients reduce their risk for atherosclerotic complications of the disease.

With the impending introduction of new generic options among the statin class of drugs, now is the time for health plans to look at their management strategies regarding this therapeutic class and their benefit design. The promotion of aggressive lipid management will become more cost-effective with the availability in the near future of generic atorvastatin, which will allow diabetic members to have access to a low-cost, high-potency statin therapy.

Health plans must act now to take advantage of this opportunity and simultaneously help improve outcomes for this ever-growing group of patients.

PATIENTS: In addition to managing blood glucose and HbA_{1c}, physicians must continue to educate diabetic patients about how to manage the risk for macrovascular complications associated with their disease. To accomplish this, diabetic patients must be informed about the importance of blood pressure management and the importance of adhering to cholesterol-lowering medication therapy for the prevention of diabetes complications seen in individuals whose lipid profile is not properly managed.

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